Food and drug rewards in humans: insights from functional brain imaging.

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Nothing in Biology Makes Sense Except in the Light of Evolution.

- Theodosius Dobzhansky (1900-1975)

Is hunger an addiction?

- Homeostasis
- Thirst determined by internal state
- Water can't be stored
- Water doesn't induce craving
- Easily available

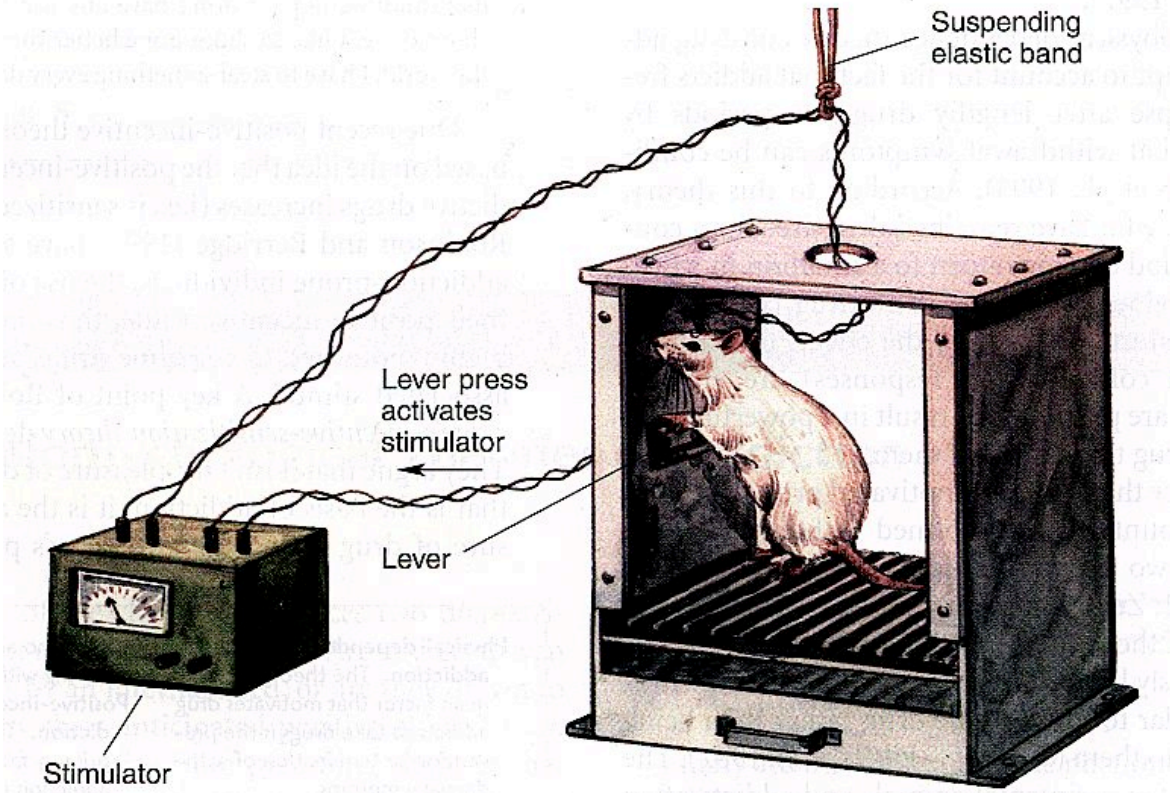
- Homeostasis does not fully explain hunger
- Calories can be stored
- Obtained through effort
- Food can induce craving even when satiated *
- Hunger is learned *

* Features of addiction

Is hunger an addiction?

- DO Hebb (1949)
  - Attributes the idea of hunger as an addiction to AJ Carlson (1916).
  - "Salted peanuts" paradox.
  - Hunger and learning:
    - Initial effect of hunger is disruptive.
    - Infant learns that eating relieves unpleasant effects (e.g. stomach contractions).
    - Eventually hunger becomes an organized behaviour
- RA Wise (1978)
  - Dopamine blockade reduces the reinforcing and rewarding effects of food.
  - Dopamine codes the "yumminess" of food.
  - Addictive drugs act on brain circuitry that originally developed to serve feeding behaviour.

Olds and Milner (1954)

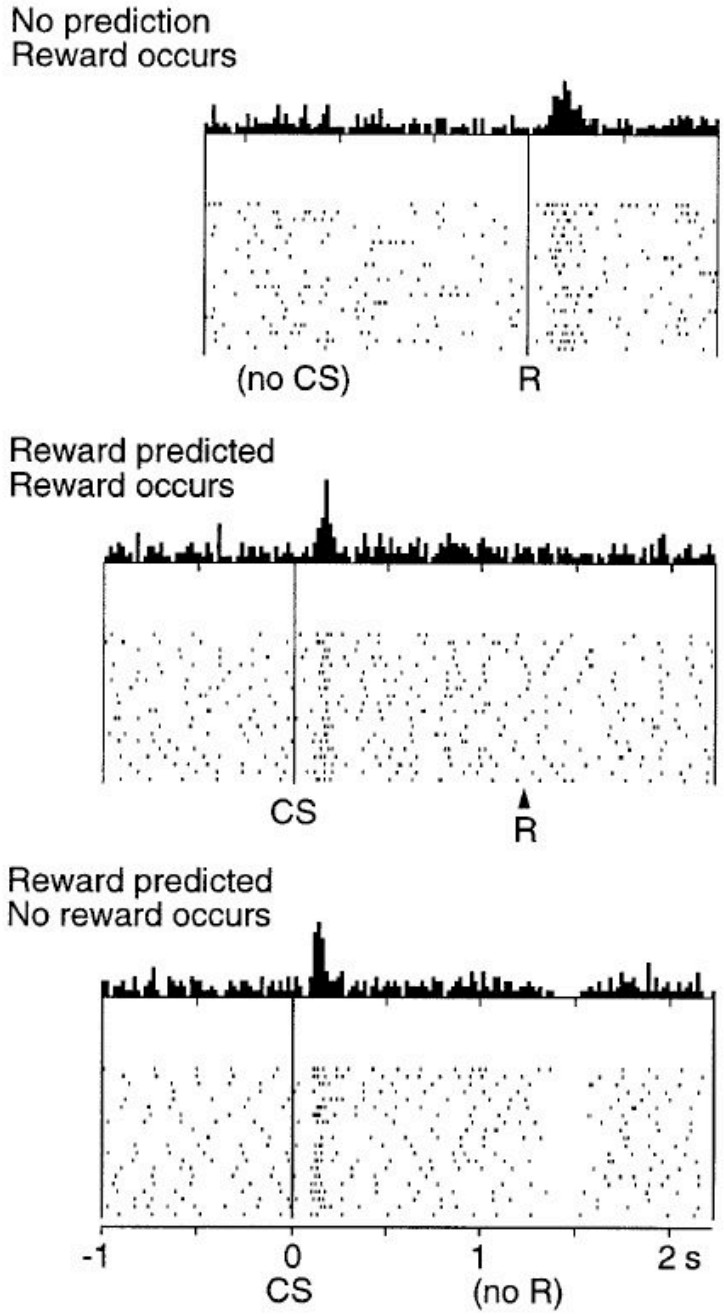


"I applied a brief train of 60-cycle sine-wave electrical current whenever the animal entered one corner of the enclosure. The animal […] came back quickly after a brief sortie which followed the second stimulation. By the time the third electrical stimulus had been applied the animal seemed indubitably to be coming back for more."
Olds, 1973, pg 31

Schultz' Model

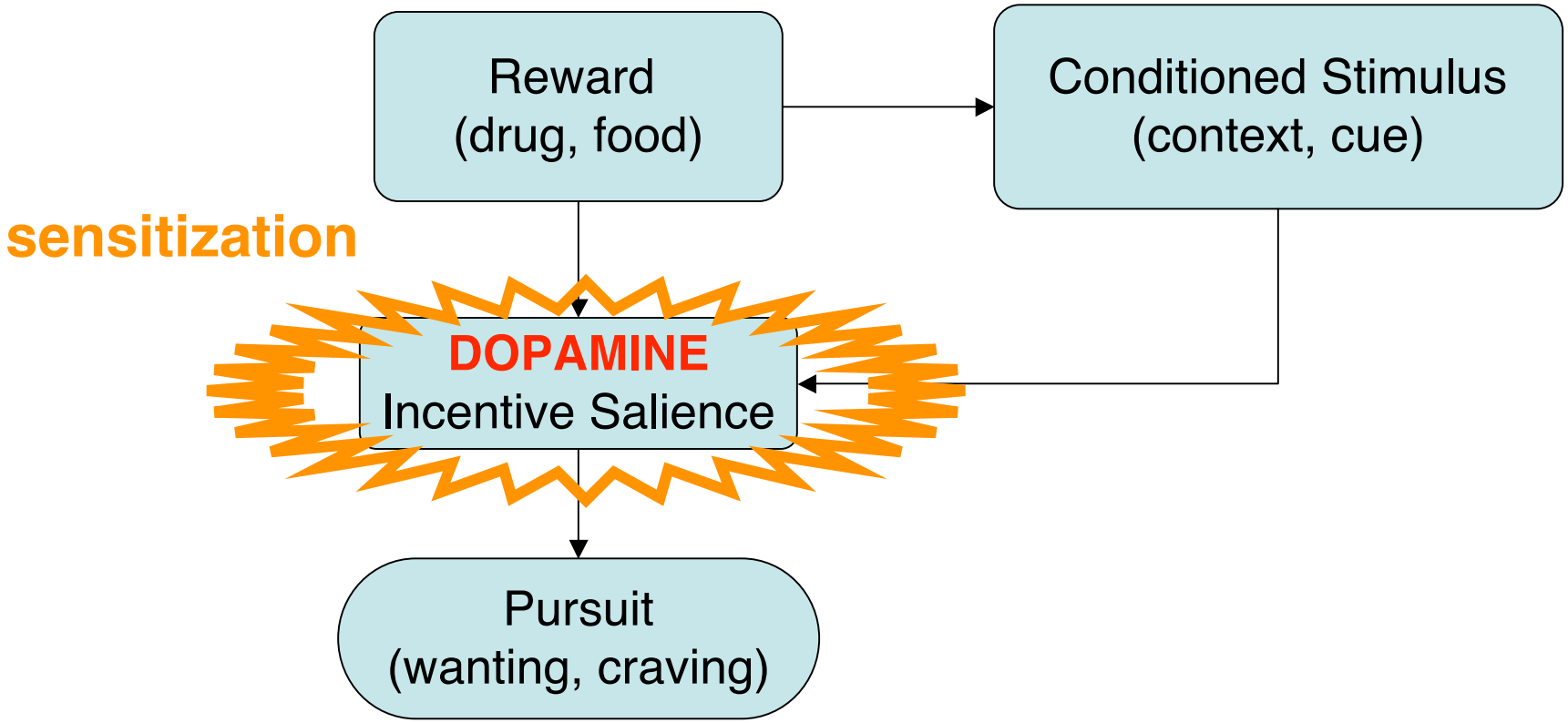
- Dopamine release:
  - Unexpected reward
  - Stimuli predicitve of reward
- No dopamine release following aversive stimuli.

DA is a learning signal that encodes the difference between expected and actual reward.



Schultz, W. J Neurophysiol. 1998.

Sensitization and addiction

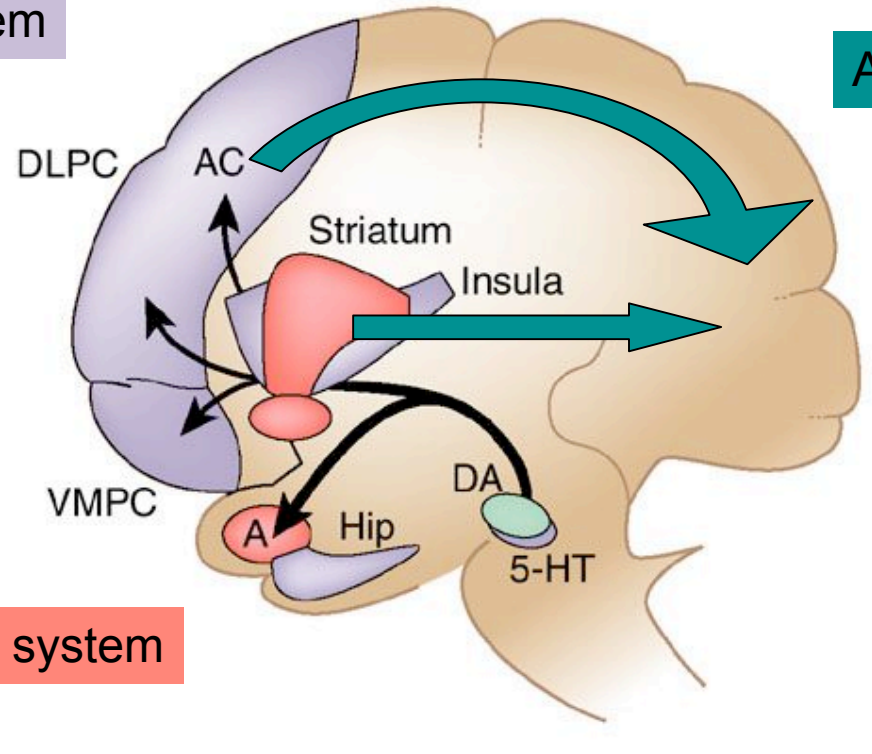


"Sensitization causes excessive cue-triggered **"wanting"** for an associated reward, which might lead to compulsive **drug pursuit** and **addiction**"

Robinson & Berridge, 1993

Compulsion and control

Reflexive system



Attention / arousal

Impulsive system

Bechara, Nat Neurosci 2005

Questions

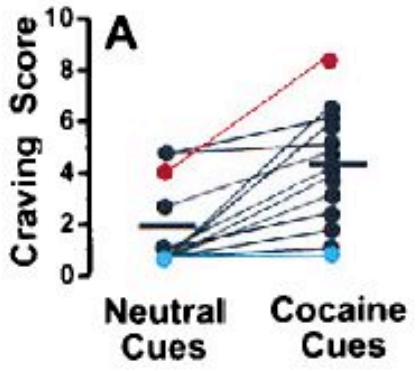
- Is the response of the dopamine system to "natural" and drug rewards similar?
- Is the dopamine system changed by drug taking / addiction?
- Are there differences in the dopamine system in individuals vulnerable to addiction.
- Interactions between frontal lobes and ascending monaminergic systems.

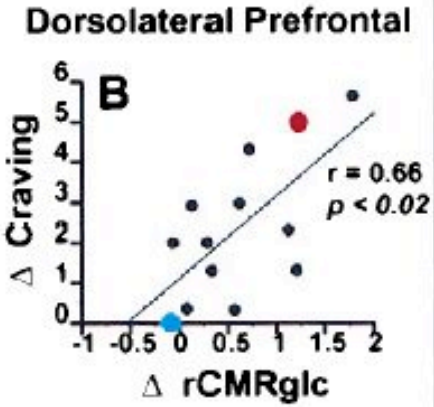
Craving

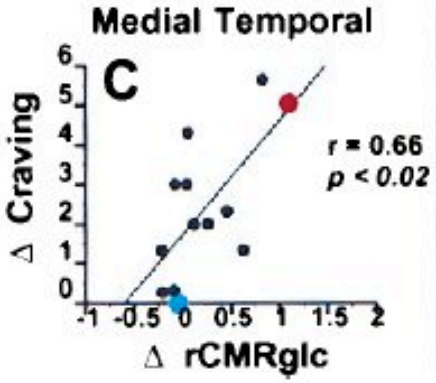
- Plays a role in relapse amongst ex-drug users.
- Often triggered by the environment in which drugs were taken.
- May involve dopamine (since dopamine antagonists may block it).
- Drug craving can be induced in a laboratory setting by cues (e.g. videos, scripts).

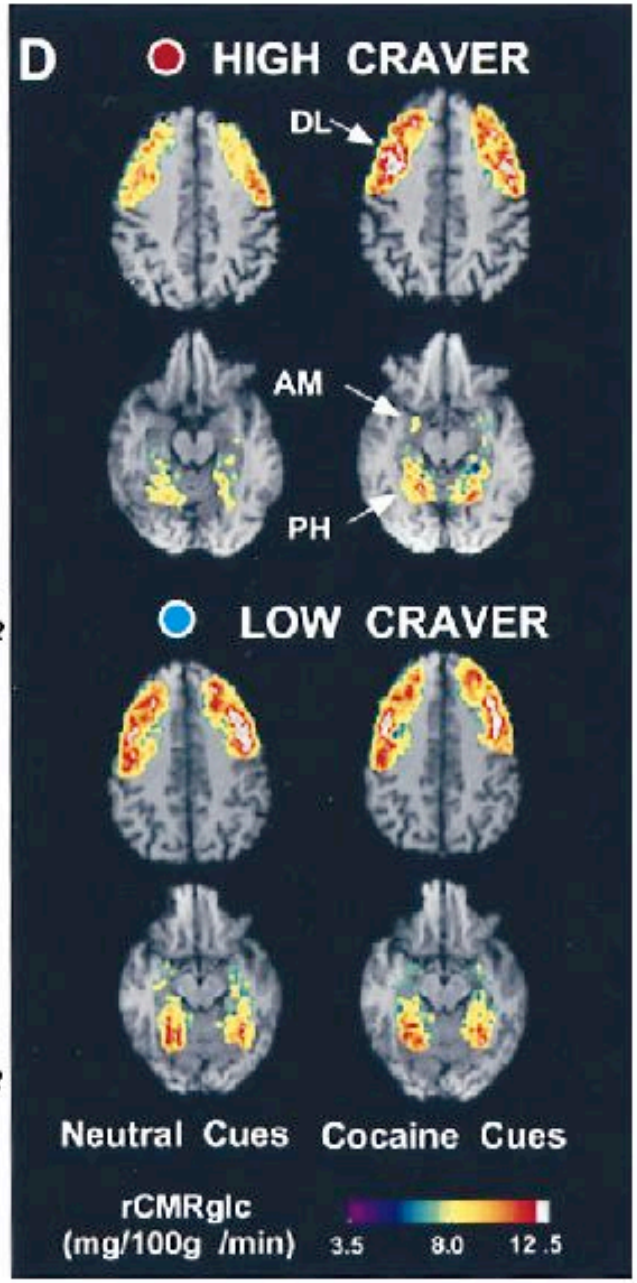
Cocaine craving (FDG PET)

- Cocaine cues compared to neutral cues.
- FDG PET to measure glucose metabolism.
- In cocaine addicts cocaine cues activate DLPFC and amygdala.









Grant et al.
PNAS 1996 93:12040-12045

Imaging studies of cue-induced craving

Table 1 Activation of DLPFC and OFC during drug-cue exposure

Study	Imaging modality	Addictive substance	Drug cue	DLPFC	OFC
Drug users currently not seeking treatment					
Bonson *et al.* (2002)	PET	Cocaine	Video, script, paraph.	Y	Y
Brody *et al.* (2002)	PET	Cigarette	Video, tactile		Y
Due *et al.* (2002)	fMRI	Cigarette	Pictures	Y	
Garavan *et al.* (2000)	fMRI	Cocaine	Video	Y	
George *et al.* (2001)	fMRI	Alcohol	Pictures, gust.	Y	
Grant *et al.* (1996)	PET	Cocaine	Video, paraph.	Y	Y
Maas *et al.* (1998)	fMRI	Cocaine	Video	Y	NA
Tapert *et al.* (2003)	fMRI	Alcohol	Pictures		Y
Tapert *et al.* (2004)	fMRI	Alcohol	Words	Y	
Wang *et al.* (1999)	PET	Cocaine	Script, tactile		Y
Drug users currently seeking treatment					
Braus *et al.* (2001)	PET	Alcohol	Video		
Childress *et al.* (1999)	PET	Cocaine	Video		
Daglish *et al.* (2001)	PET	Opiate	Script		
Kilts *et al.* (2001)	PET	Cocaine	Script		
Schneider *et al.* (2001)	fMRI	Alcohol	Olfact.		
Modell *et al.* (1995)	SPECT	Alcohol	Gust., olfact.		
Sell *et al.* (1999)	PET	Opiate	Video, drug		
Wexler *et al.* (2001)	fMRI	Cocaine	Video		
Wrase *et al.* (2002)	fMRI	Alcohol	Pictures	Y	Y

Wilson et al. Nat Neurosci

A fMRI study of cigarette craving

Neutral Videos

Smoking Videos

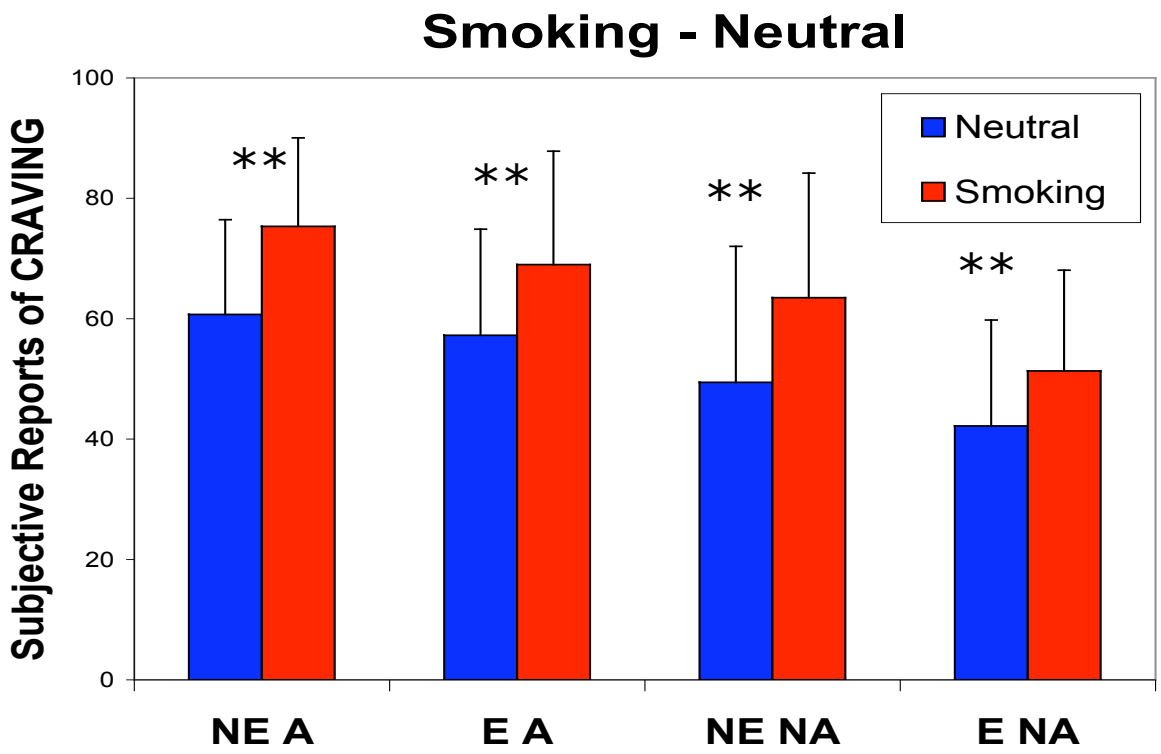
20 SUBJECTS

-Right-handed
-10 Male
-10 Female
-2 scans (one month apart)

	ABSTINENT	NON-ABSTINENT
EXPECTANT GROUP (10)	- No smoking 12 hrs. prior to scan - Smoke after scan	- Smoke before and after scan
NON-EXPECTANT GROUP (10)	- No smoking 12 hrs. prior to, or 4 hrs. after scan	- Smoke before scan but no smoking 4 hours after scan

McBride et al. Neuropsychopharm 2006

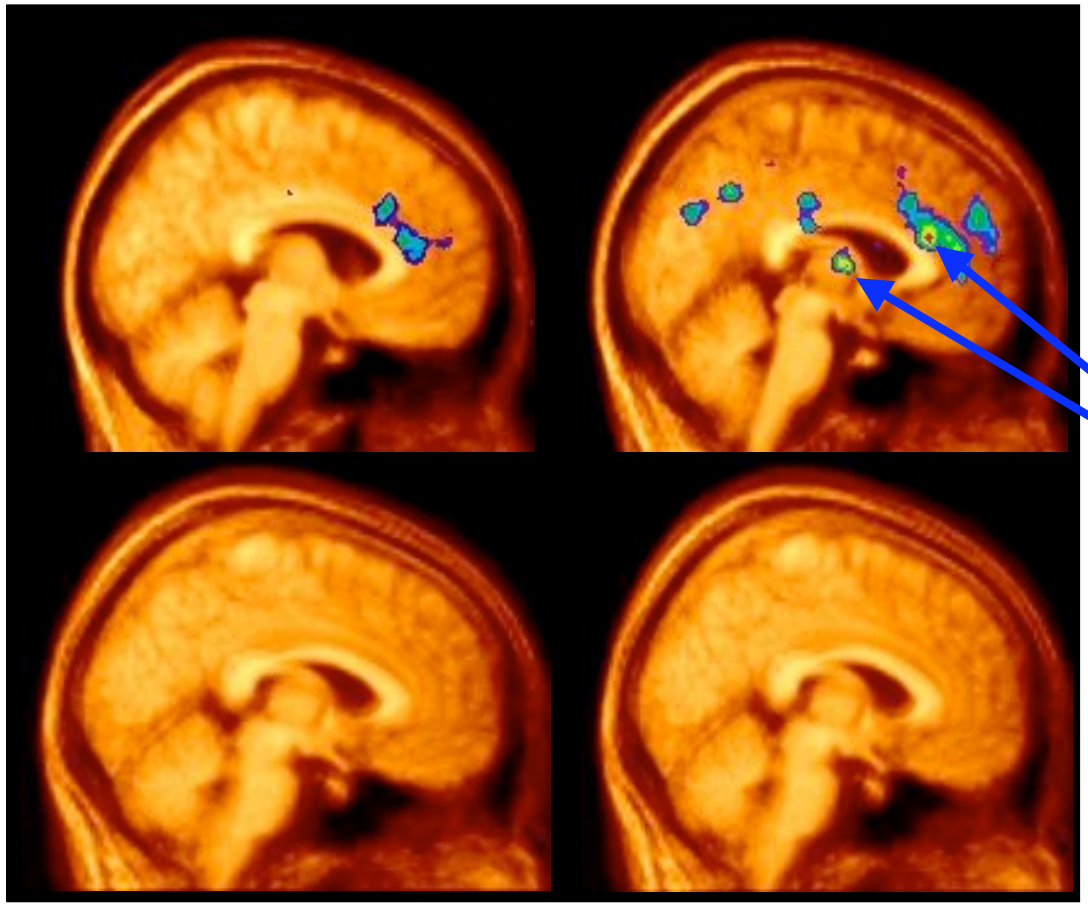
Craving reports



McBride et al. Neuropsychopharm 2006

Effect of expectancy / abstinence

Smoking video > Haircut video



Lack of activation in non-expectant condition: inhibition of response to conditioned cues?

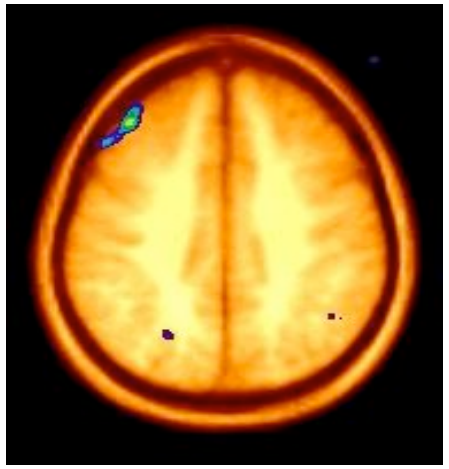
Ascending Reticular Activating System

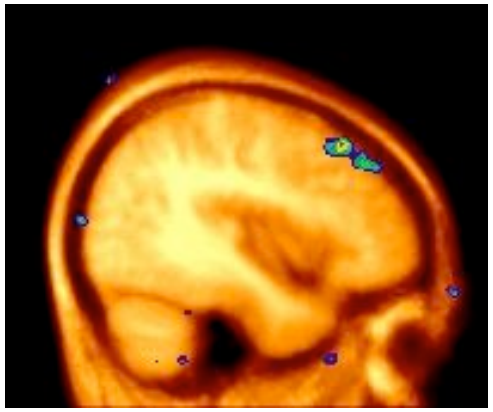
(AROUSAL)

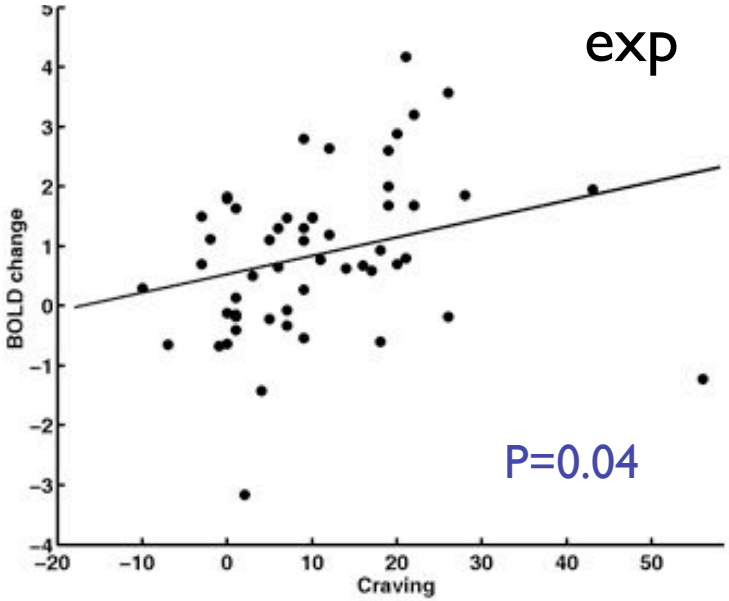
McBride et al. Neuropsychopharm 2006

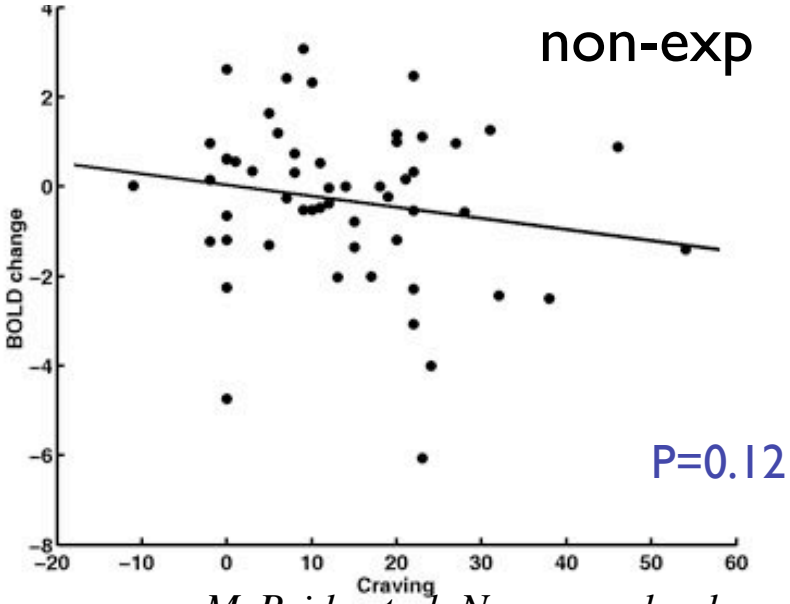
Expectancy effects

- DLPFC (20, 58, 34)
  - Exp - Nonexp
  - Affected by craving, as in previous studies.





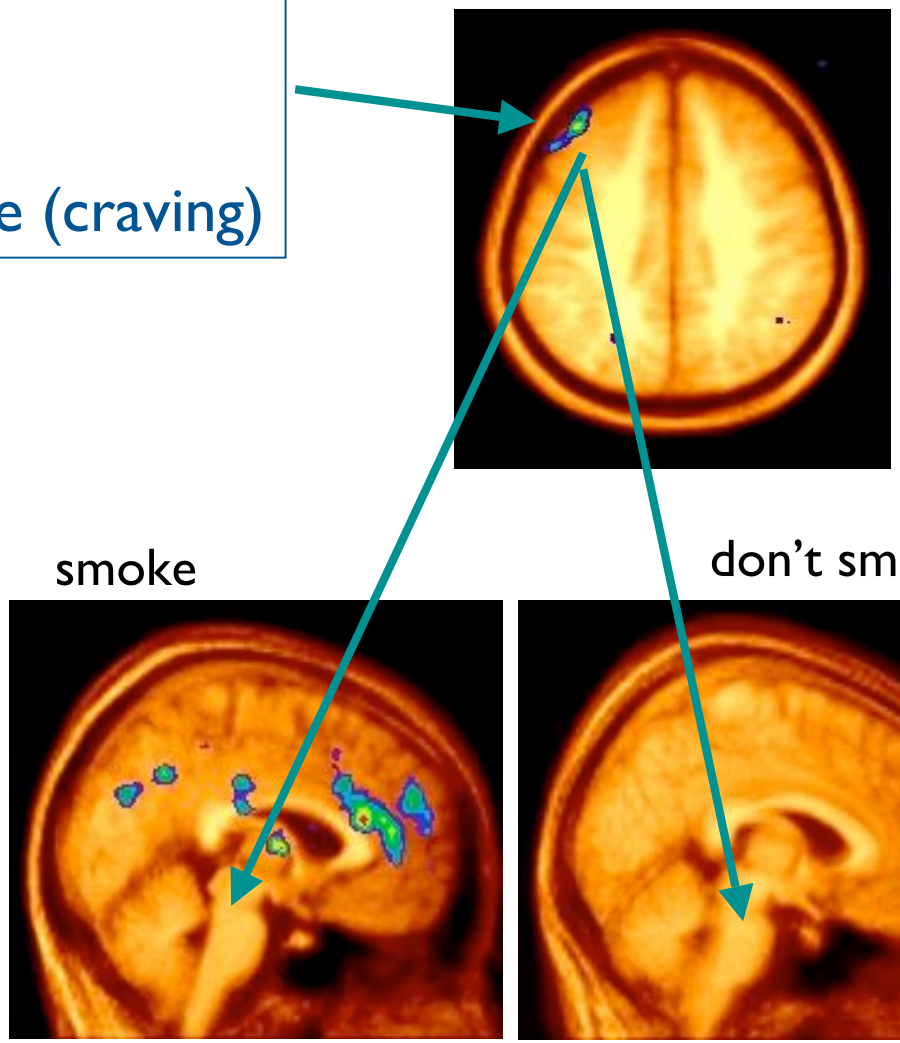




McBride et al. Neuropsychopharm 2006

Expectancy affects DLPFC response

- Contingency
- Context
- Cue
- Internal state (craving)



- Stress
- Alcohol
- Nicotine

McBride et al. Neuropsychopharm 2006

Effect of stress

1)

Stress task

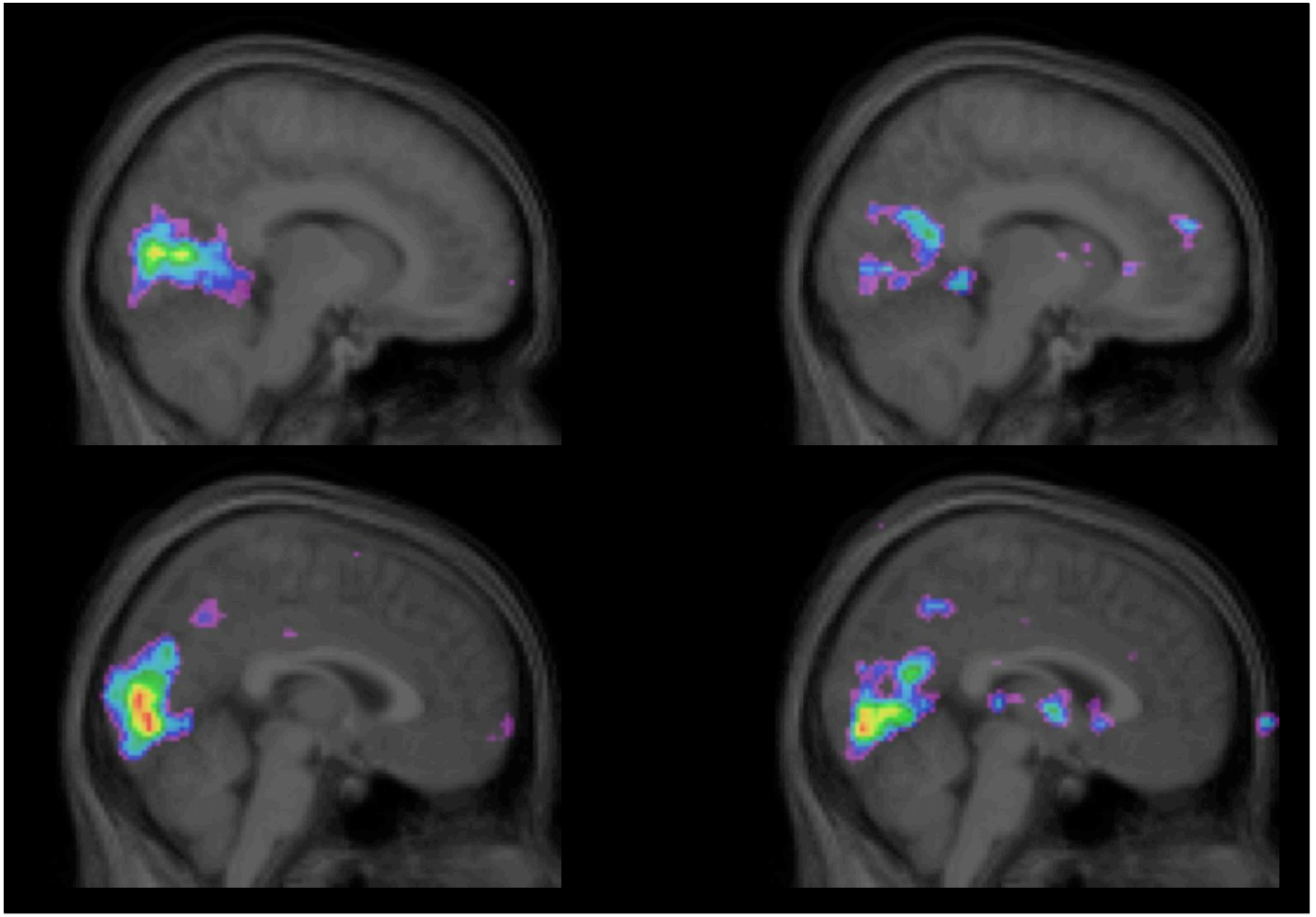
2)

Control task

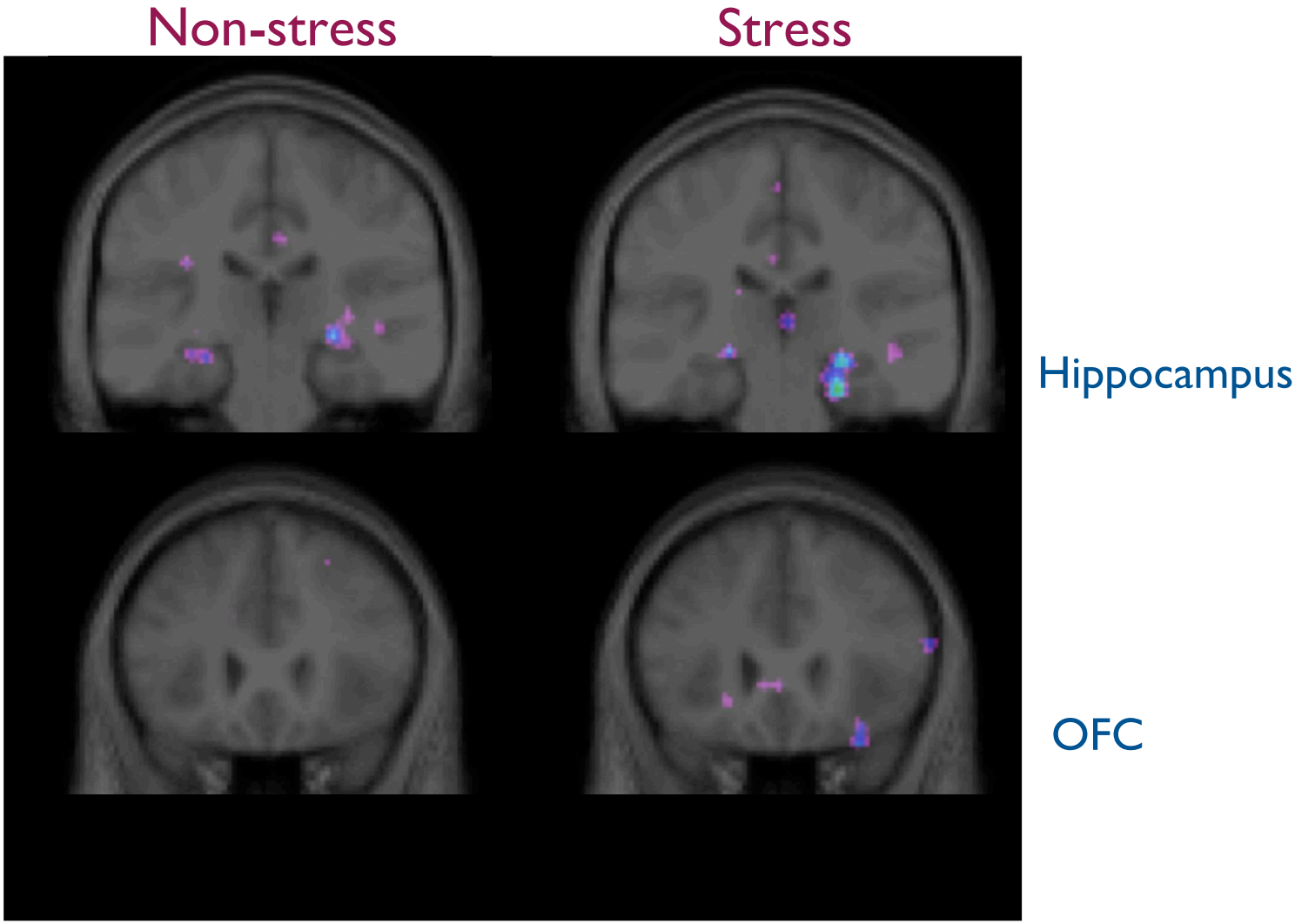
Effect of stress

Non-stress

Stress



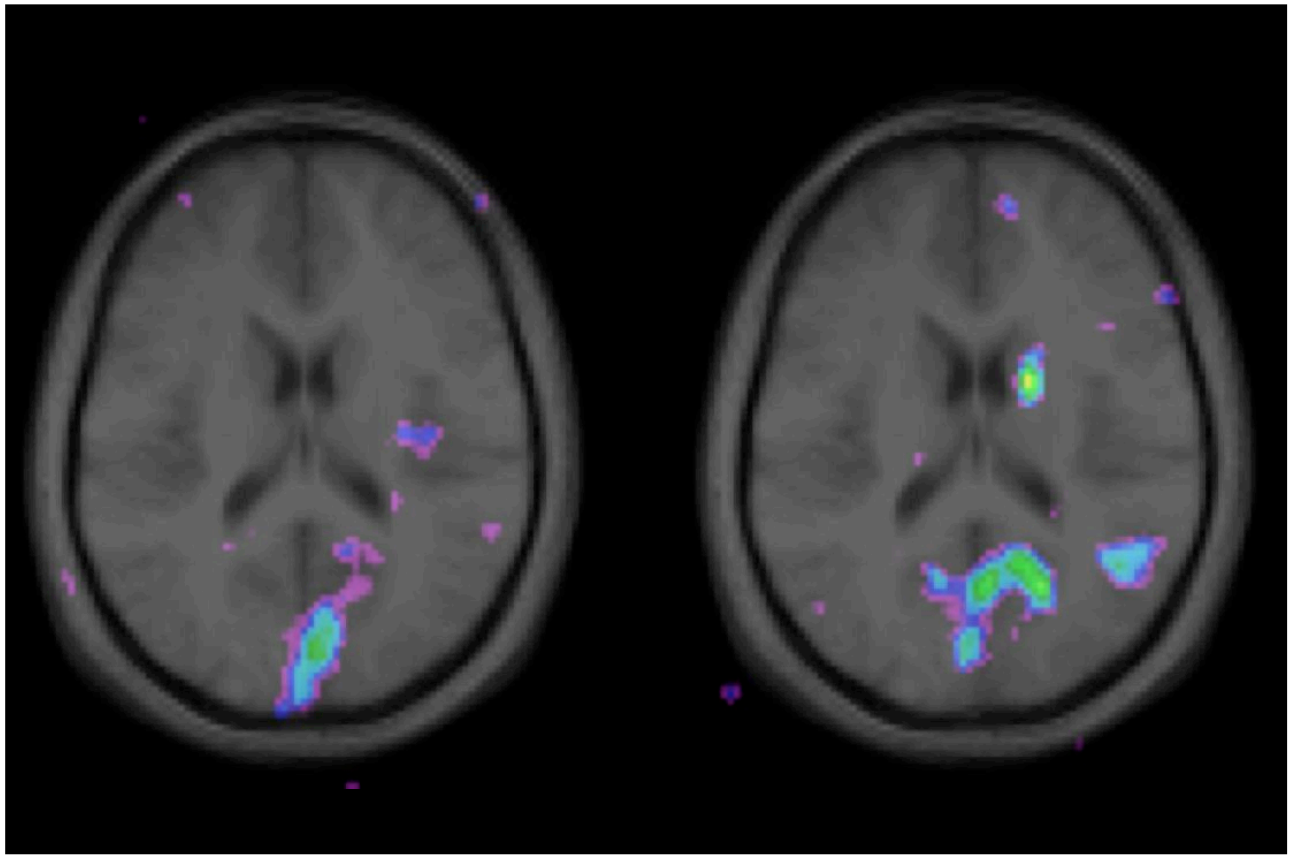
Effect of stress



Effect of stress

Non-stress

Stress



Caudate

Cue-induced brain activation

- ACC, mPFC, dorsomedial thalamus
  - Activated during expectancy only
  - Arousal, Attention, Self-referential emotions
- DL-PFC
  - Modulated by expectancy and craving
  - Activity reflects influence of internal state, motivation and drive, external contingencies.
  - May be involved in planning to smoke and in over-riding the urge to smoke, depending on context.
- Role of cues
  - Cigarette cues are arousing, especially when cigarettes are available.

Brain response to “food cues”

- Event-related fMRI
- Images displayed 5s, 15s apart.






Food minus scenery (hungry subjects)

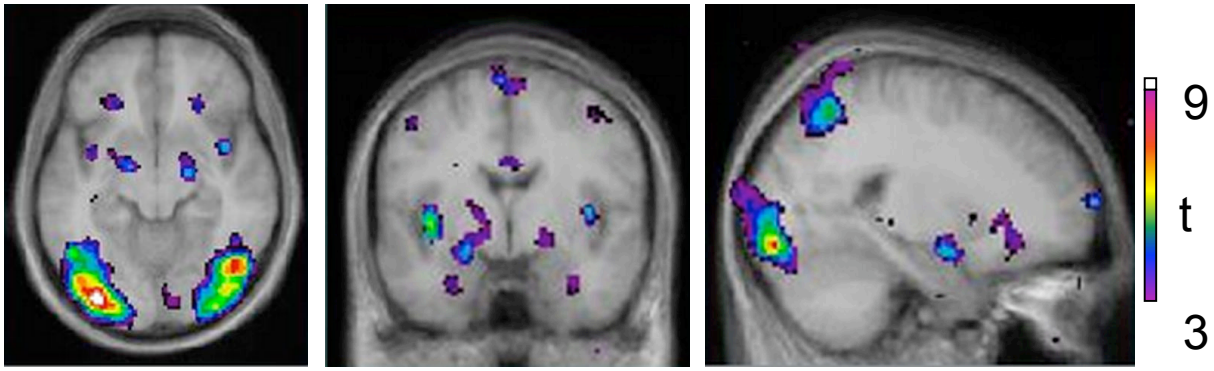
OFC *

Amygdala

Insula *

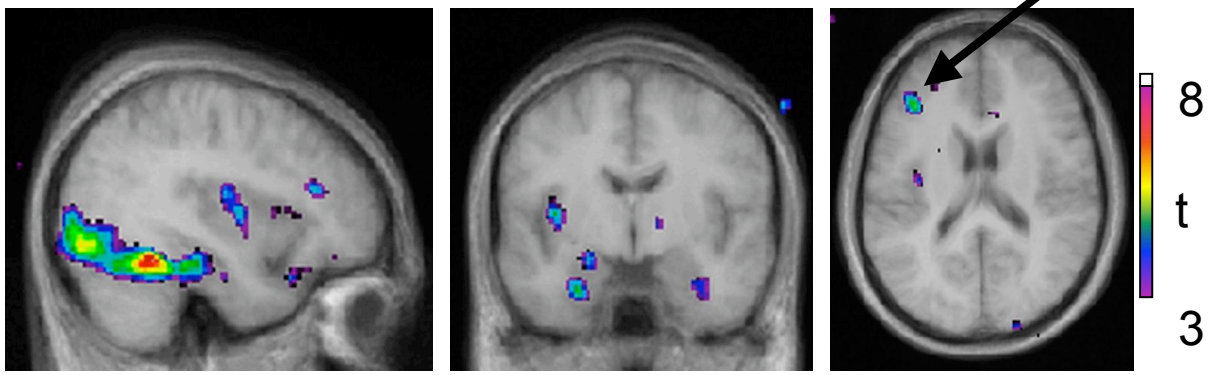
Visual

Expecting to eat

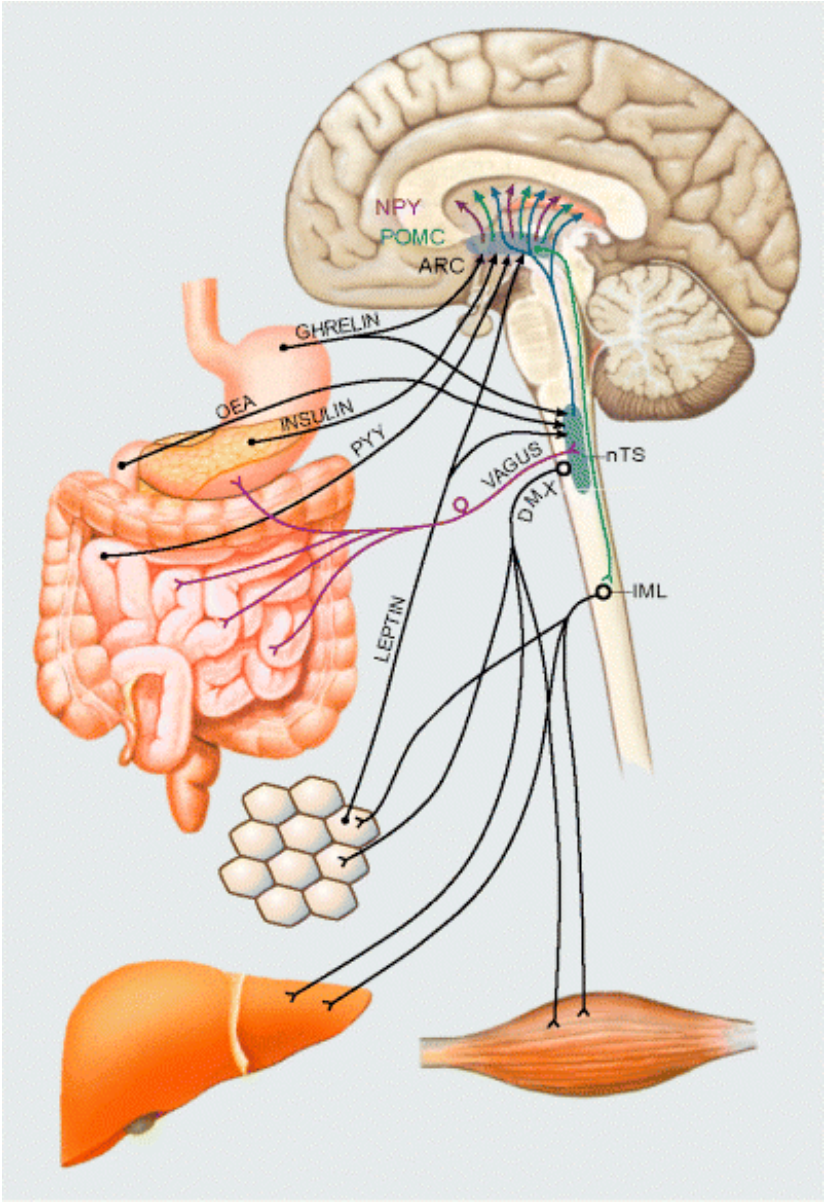


Expecting not to eat

lateral PFC

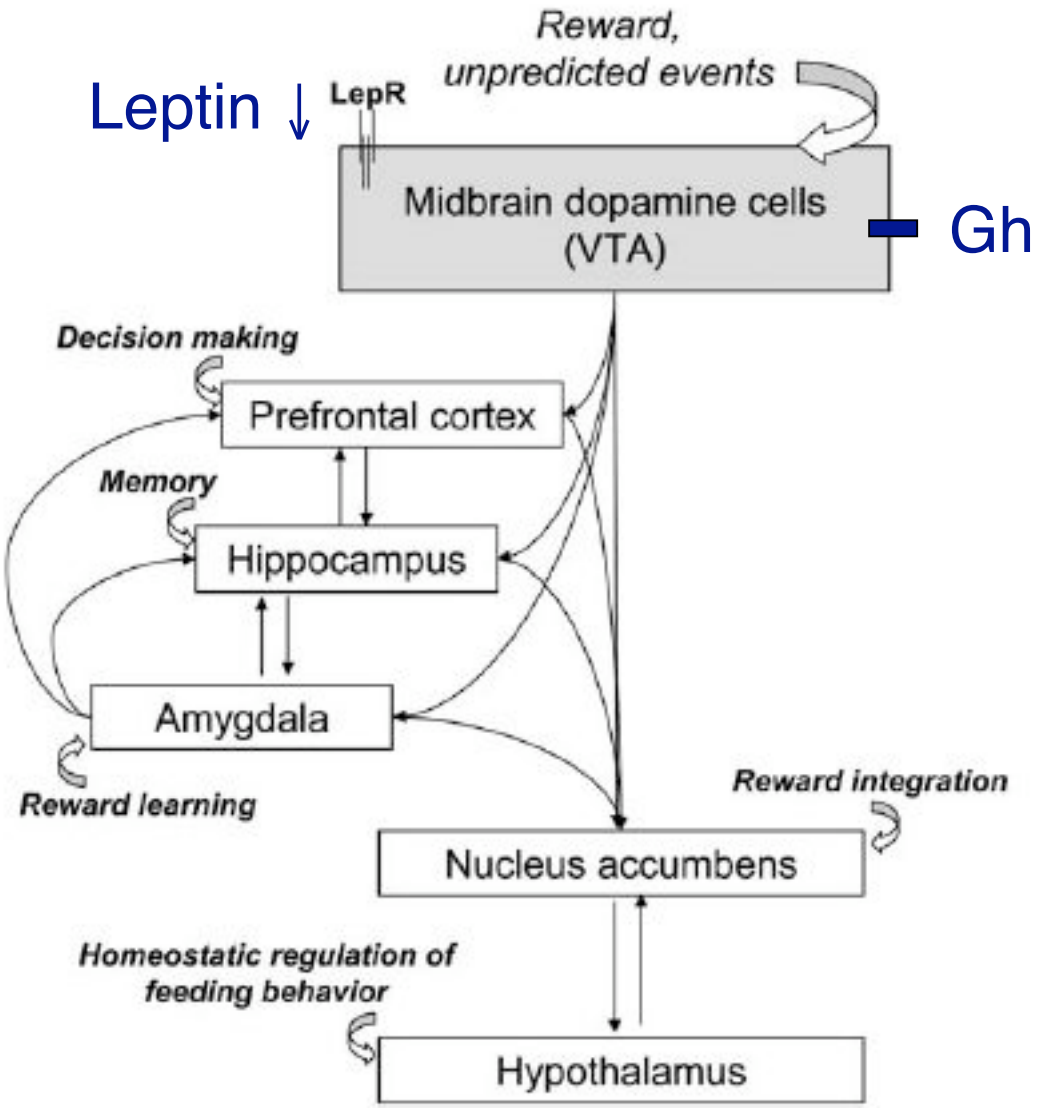


Gut - brain interactions



Broberger
J Intern Med 2005

Gut - brain interactions

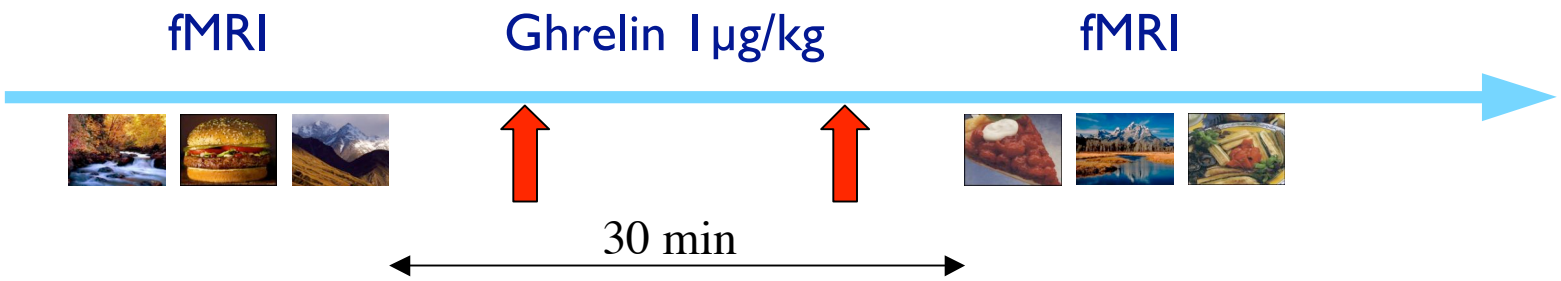


Cota et al.
Neuron 2006

Abizaid et al.
JCI 2006

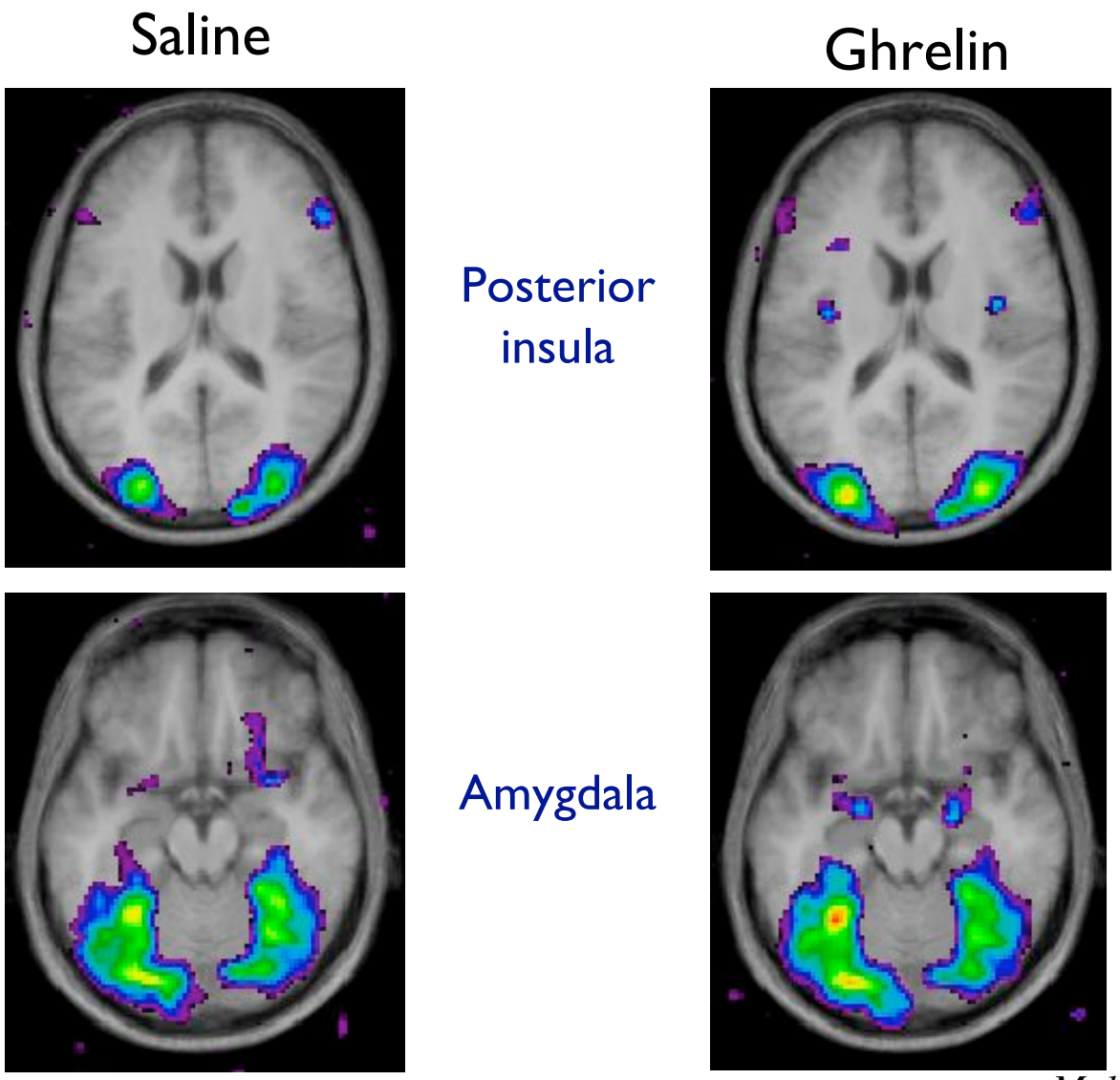
Effect of ghrelin

- Ghrelin is an orexigenic peptide hormone
- Increases hunger and food intake
- Acts on hypothalamus, but there is increasing evidence that it also acts directly on other areas: dopamine neurons, hippocampus…
- 12 non-hungry subjects tested:



Malik et al. submitted

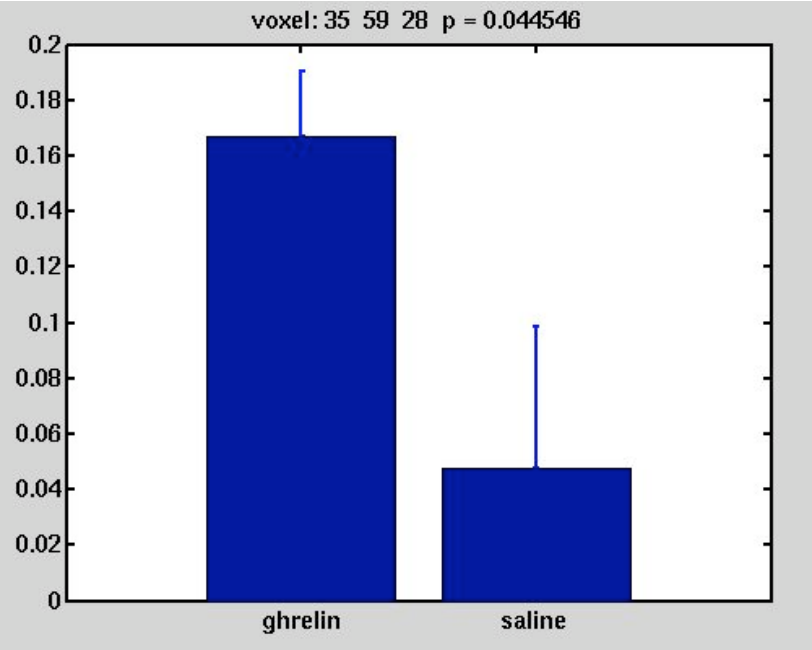
Effect of ghrelin on response to food pictures



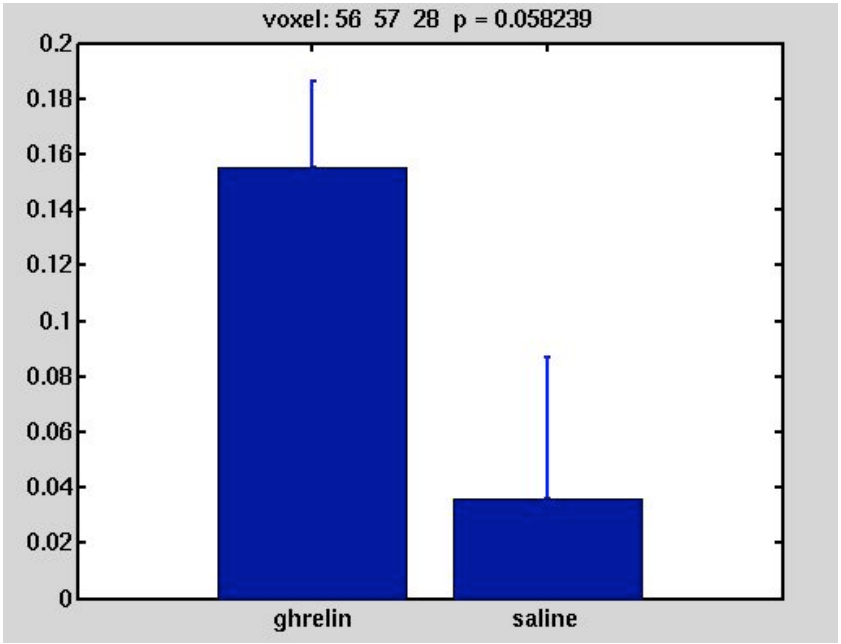
Malik et al. submitted

Food pictures minus baseline

Left amygdala



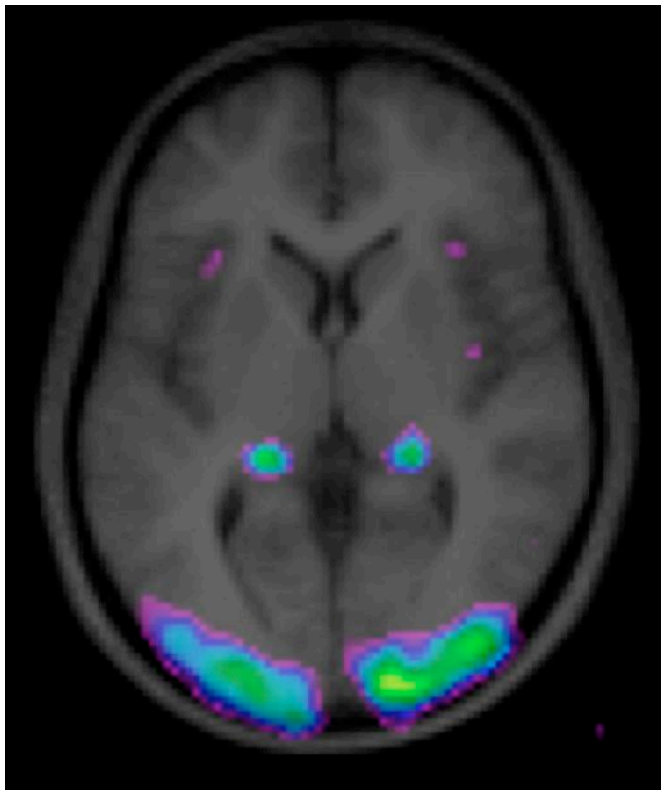
Right amygdala



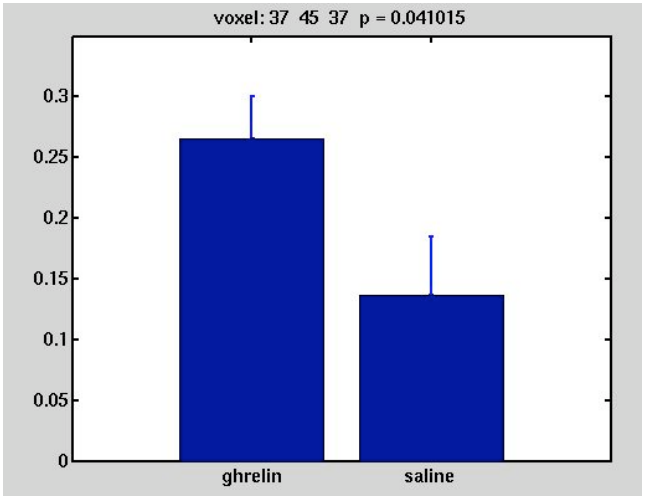
Increase in amygdala activation correlates with increase in hunger

Malik et al. submitted

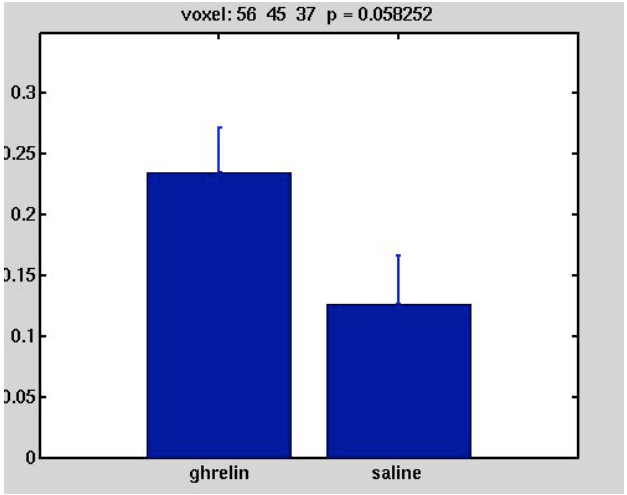
Ghrelin effects on visual areas



Left pulvinar



Right pulvinar



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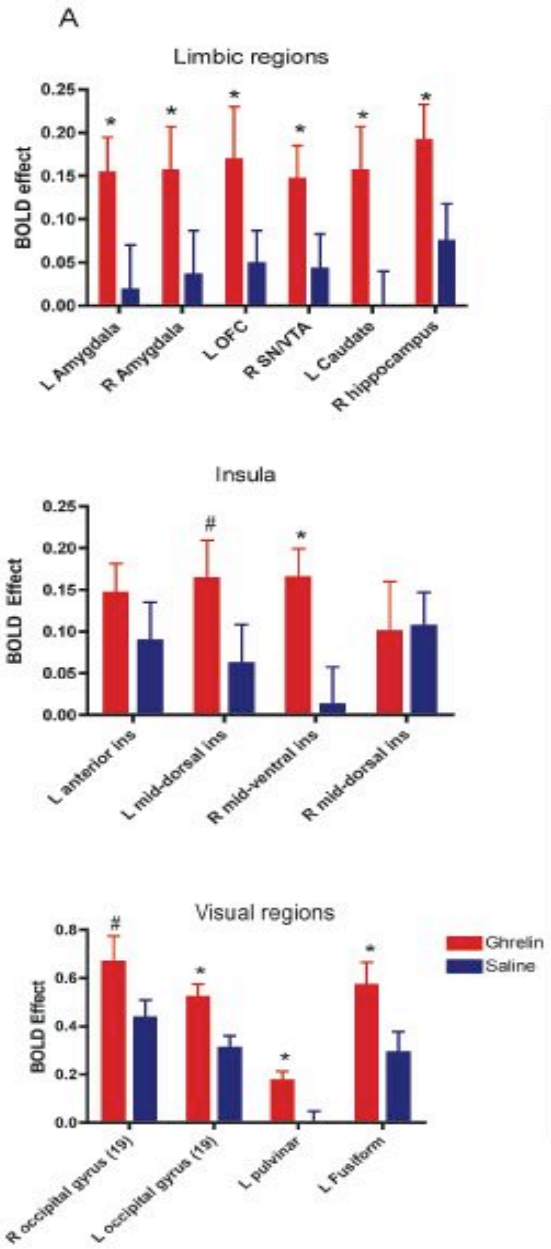
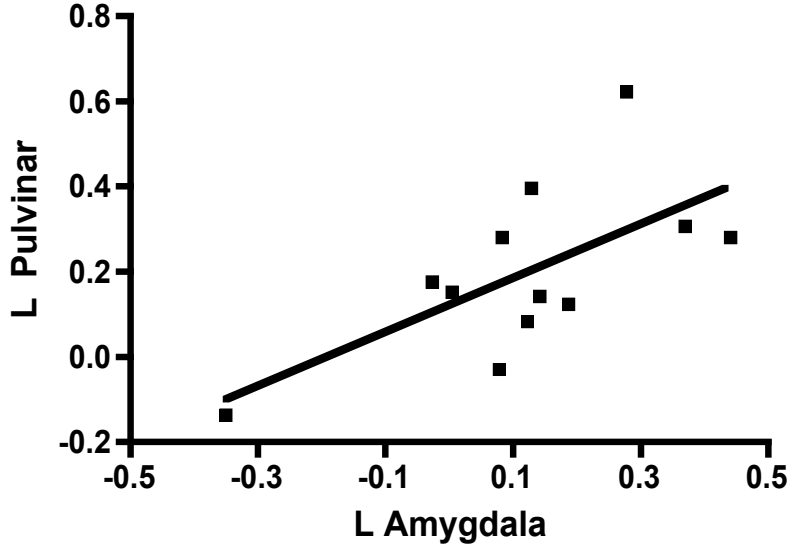
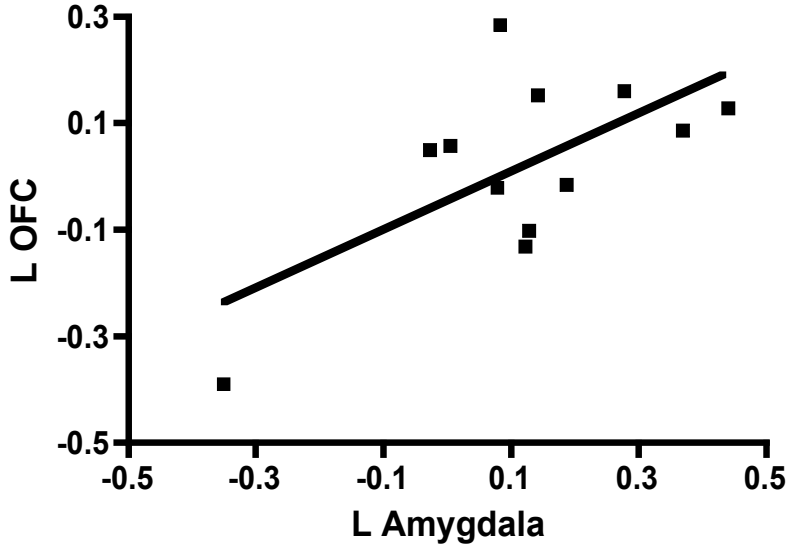
Ghrelin effects



Malik et al. submitted

Ghrelin effect - correlations





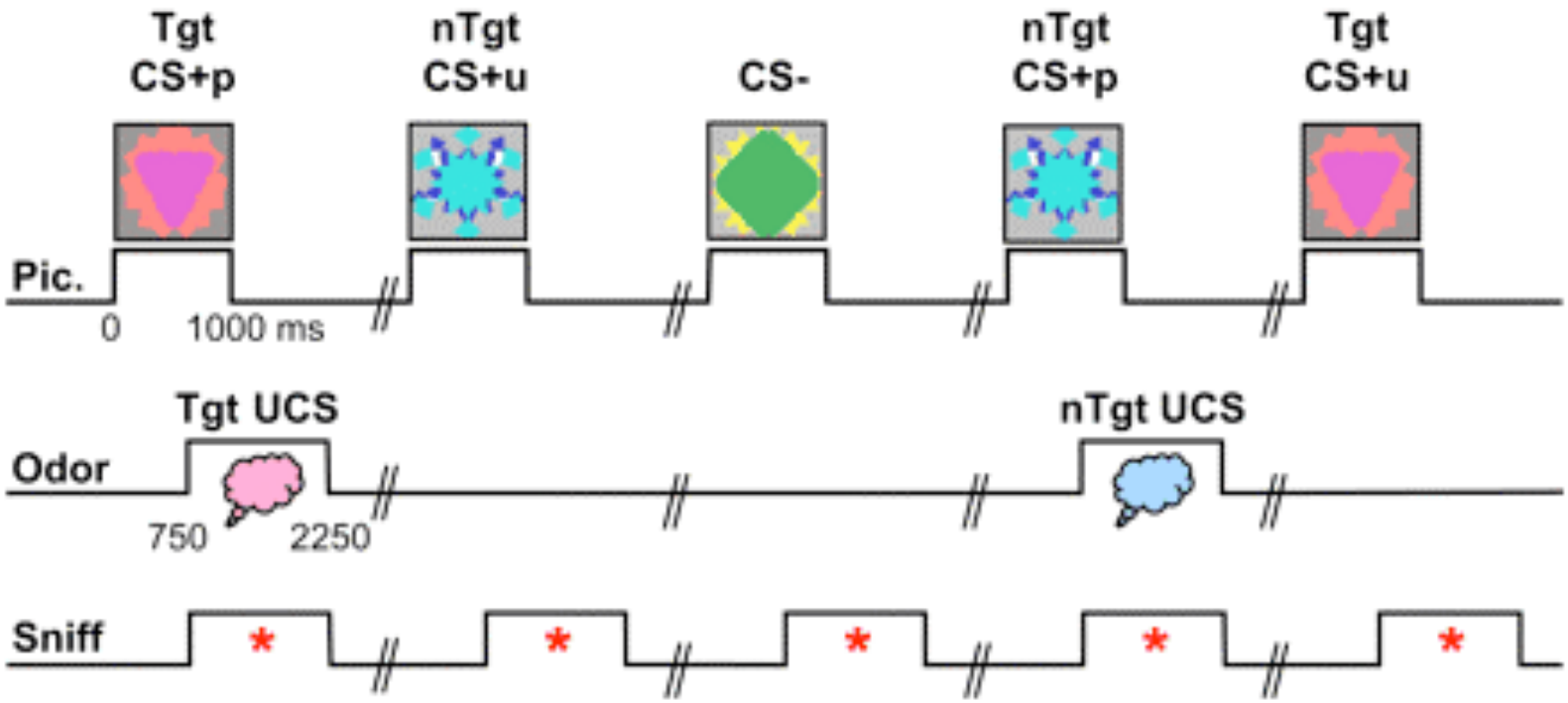
Malik et al. submitted

Food picture recall and rating

	Pictures seen in the **saline** condition	Pictures seen in the **ghrelin** condition	P-value
Recall task (Did you see this food picture in the scanner?)	81.8 ± 10.8	88.8 ± 7.3	0.014*
Picture rating task (Rate picture on a scale of 1- 9)	6.7 ± 0.84	6.8 ± 0.88	0.479

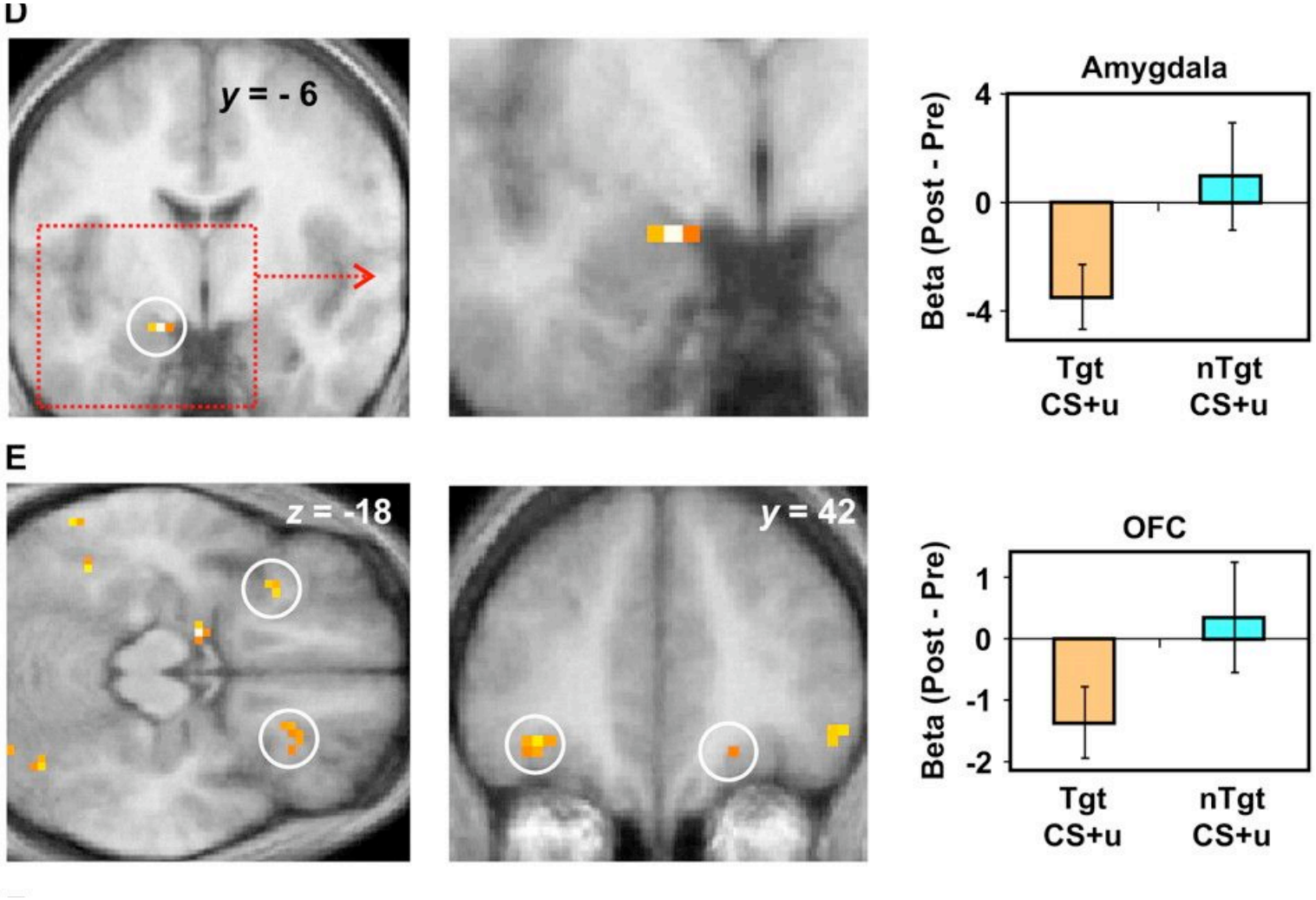
Malik et al. submitted

Amygdala/OFC: predictive hedonic evaluation



Gottfried et al. Science 2003

Amygdala/OFC: predictive hedonic evaluation



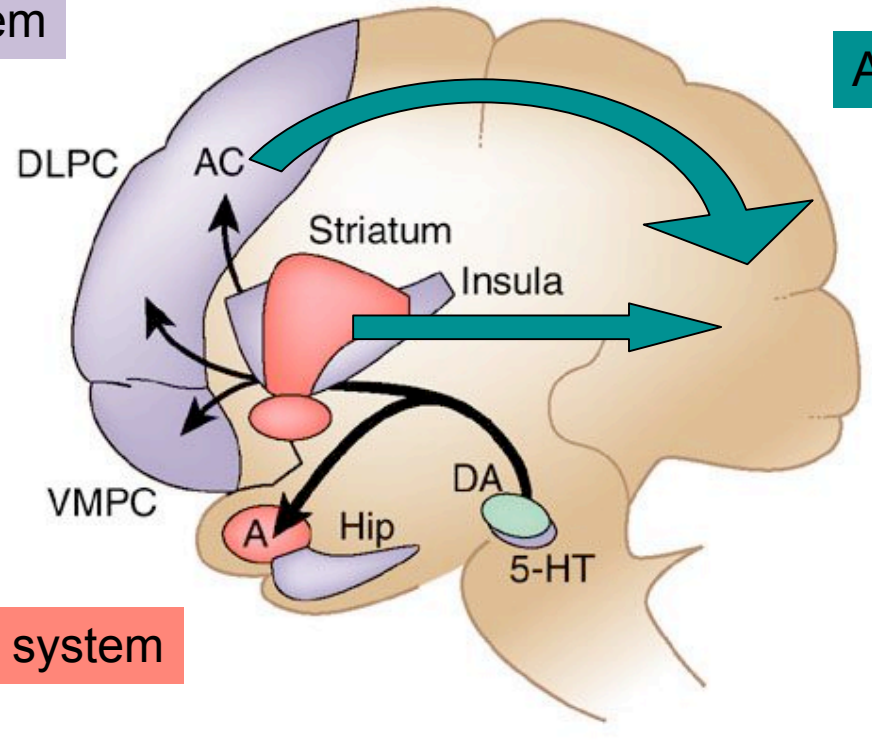
Gottfried et al. Science 2003

Ghrelin

- A “metabolic” feeding signal.
- Increases response to food cues in brain areas involved in motivation, hedonic evaluation, memory.
- “Incentive salience”.
- Metabolic feeding signals act on hedonics and motivation.

Compulsion and control

Reflexive system



Attention / arousal

Impulsive system

Bechara, Nat Neurosci 2005